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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
COLLINS, CYNTHIA E	

ART UNIT	PAPER NUMBER
1638	

DATE MAILED: 01/31/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/673,710	BURSSENS ET AL.	
	Examiner	Art Unit	
	Cynthia Collins	1638	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 October 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,5,6,10,11,13-16,18-20,22-26,28,29 and 31* is/are pending in the application.

4a) Of the above claim(s) *13-16* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,5,6,10,11,18-20,22-26,28,29 and 31* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on June 28, 2004 has been entered.

The Amendment filed October 20, 2004 has been entered.

Claims 2-4, 7-9, 12, 17, 21, 27 and 30 are cancelled.

Claims 23, 25 and 31 are currently amended.

Claims 1, 5-6, 10-11, 13-16, 18-20, 22-26, 28-29 and 31 are pending.

Claims 13-16 are withdrawn.

Claims 1, 5-6, 10-11, 18-20, 22-26, 28-29 and 31 examined.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

All previous objections and rejections not set forth below have been withdrawn.

Claim Rejections - 35 USC § 112

Claims 1, 5-6, 10-11, 18-20, 22-26, 28-29 and 31 remain rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time

the application was filed, had possession of the claimed invention, for the reasons of record set forth in the office action mailed February 24, 2004.

Applicant's arguments filed June 28, 2004 have been fully considered but they are not persuasive.

Applicants submit that the specification discloses different nucleic acid molecules encoding a CDK which may be introduced into a plant in order to confer stress tolerance, and Applicants further submit that they have exemplified one nucleic acid molecule which when introduced into a plant confer stress tolerance, that being a nucleic acid molecule encoding an Arabidopsis CDC2a (CDKA;1) mutein wherein the tyrosine at position 15 is substituted to phenylalanine and the threonine at position 14 is substituted to alanine. Applicants point out that is well-established that the law construing 35 U.S.C. 112, first paragraph, does not require a specific example of everything within the scope of the broad claims, and that in fact, the law does not require any specific working examples. Applicants further point to *In re Robbins* which states that "if the Examiner and/or Board intended a rejection under the first paragraph of §112 it must be reversed, inasmuch as the specification contains a statement of Appellant's invention which is as broad as Appellant's broadest claims..." *In re Robbins*, 429 F.2d 452, 456, 166 USPQ 552, 555 (CCPA 1970). (reply page 7)

The Examiner maintains that the outstanding written description rejection was not predicated on the failure of the specification to exemplify nucleic acids. The outstanding written description rejection was predicated on the failure of the specification to describe the genus of CDK muteins encoded by the nucleic acid molecules encompassed by the claims (pages 3-4 of the office action mailed February 24, 2004; pages 4-5 of the office action mailed June 3, 2003).

In this regard *In re Robbins* is inapposite to the outstanding rejection as *In re Robbins* concerned the description of nonanalogous compounds, i.e. "ionizable, halogen-free monoorgano mercuric compounds". Naming a nucleic acid compound does not describe a nucleic acid compound, and sequences that are not known or disclosed at the time of filing are not considered to be described. See *University of California v. Eli Lilly,* 43 USPQ 2d 1398, 1406 (Fed. Cir. 1997), where it states: naming a type of material generally known to exist, in the absence of knowledge as to what that material consists of, is not a description of that material. Thus, as we have previously held, a cDNA is not defined or described by the mere name "cDNA," even if accompanied by the name of the protein that it encodes, but requires a kind of specificity usually achieved by means of the recitation of the sequence of nucleotides that make up the cDNA. *See Fiers,* 984 F.2d at 1171, 25 USPQ2d at 1606.

Applicants also submit that the Examiner appears to predicate the written description rejection on the fact that the specification does not describe or characterize other non phosphorylatable amino acid residues that may occupy the positions corresponding to residues 14 and 15 respectively in *Arabidopsis thaliana* CDKA;1 as claimed in claims 1 and 5. Applicants submit that one skilled in the art would be aware of other non-phosphorylatable amino acid residues that could be substituted for the phosphorylatable tyrosine or threonine, since this information was available in the prior art as of the priority date of the present application. Applicants point in particular to Exhibit A, page 84 from Molecular Biology of the Cell, 2d ed., 1989, Bruce Alberts, et al., Garland Publishing, Inc., New York, N.Y., under the heading "Enzymes Can Be Switched On and Off by Covalent Modification", where the authors

write: "[c]ells have different devices for regulating when longer lasting changes in activity, occurring over minutes or hours, are required. These involve reversible covalent modification of enzymes, which is often, but not always, accomplished by the addition of a phosphate group to a specific serine, threonine, or tyrosine residue in the enzyme. The phosphate comes from ATP, and its transfer is catalyzed by a family of enzymes known as protein kinases." Applicants maintain that the present application is directed to such a protein kinase, and that the present invention is specifically directed to methods of using mutant cyclin dependent kinases (CDKs) comprising a PSTAIR cyclin binding motif, vectors comprising nucleic acid molecules encoding such mutant CDKS, and transgenic plants and plant parts comprising such nucleic acid molecules wherein the CDK muteins are not susceptible to inhibitory phosphorylation under certain stress conditions due to the substitution of a non-phosphorylatable amino acid in place of either a tyrosine at a position that corresponds to the tyrosine located at position 15 in the amino acid sequence of *A. thaliana* CDKA;1, or for both this tyrosine and a threonine located at a position that corresponds to the threonine located at position 14 in the amino acid sequence of *A. thaliana* CDKA;1. (reply pages 7-8).

The Examiner maintains that a general awareness on the part of one skilled in the art of other non-phosphorylatable amino acid residues that could be substituted for phosphorylatable tyrosine or threonine residues in a protein kinase does not substitute for a description of the non-phosphorylatable amino acid residues that can be substituted for the phosphorylatable tyrosine or threonine residues that occupy the positions corresponding to residues 14 and 15 respectively in *Arabidopsis thaliana* CDKA;1 such that the resultant CDK muteins are not susceptible to inhibitory phosphorylation under certain stress conditions and such that the resultant CDK

muteins confer drought or salt stress tolerance to a plant, as the functional effect of amino acid substitution, including the substitution of non-phosphorylatable amino acids for phosphorylatable amino acids, will vary depending on the amino acid sequence of the protein, the position of the substituted amino acid in the sequence, and the amino acid substituted (See Krek W. et al. and Gould K.L. et al. set forth below). While the submitted reference of Alberts et al. (Exhibit A) teaches that protein kinases may covalently modify enzymes by the addition of a phosphate group to a specific serine, threonine, or tyrosine residue in the enzyme, Alberts et al. (Exhibit A) do not describe the non-phosphorylatable amino acid residues that can be substituted for the phosphorylatable tyrosine or threonine residues that occupy the positions corresponding to residues 14 and 15 respectively in *Arabidopsis thaliana* CDKA;1.

Applicants further submit that as of the priority date of the present application, it was widely known which types of substitutions were more favorable than others for the phosphorylatable tyrosine or threonine. Applicants point in particular to Exhibit B, M.J. Betts and R.B. Russel, Amino acid properties and consequences of substitutions in Bioinformatics for Geneticists, M.R. Barnes, I.C. Gray eds, Wiley, 2003, and Applicants point out that although the book was published in 2003, much of the text of Bioinformatics for Geneticists contains information that has been published prior to the April 21, 1998 priority date of the present application, including the information provided at Exhibit B. Applicants point out that, as indicated in Exhibit B, substitution preferences for tyrosine for all protein types including intracellular proteins into which CDKS would fall, are listed as Phe, Trp, or His, and one skilled in the art would thus likely consider substituting Phe, Trp, or His for tyrosine in place of

tyrosine, in the first instance. Applicants maintain that Leu, Cys, Val, Ile, and Met would also be considered since these amino acids are considered to constitute a neutral change for Tyrosine. Again referring to Exhibit B, with respect to threonine, Applicants point out that while in all protein types serine substitution is favored, since serine is also phosphorylatable, one skilled in the art practicing the present invention would not choose to substitute serine for a threonine. Applicants point out that, as indicated in Exhibit B, one skilled in the art wishing to substitute a non-phosphorylatable amino acid for threonine would in the first instance consider Ala, Asn, or Val, and that with respect to intracellular proteins, into which CDKS would fall, one skilled in the art would also consider substituting for Threonine Cys, Asp, Glu, Lys, Met, His, Ile, Asn, Pro, Gln, Arg, Ser, Ala, or Val. (reply pages 8-9)

The Examiner maintains that a general knowledge of which types of substitutions are more favorable than others for the phosphorylatable tyrosine or threonine does not substitute for a description of the non-phosphorylatable amino acid residues that can be substituted for the phosphorylatable tyrosine or threonine residues that occupy the positions corresponding to residues 14 and 15 respectively in *Arabidopsis thaliana* CDKA;1 such that the resultant CDK muteins are not susceptible to inhibitory phosphorylation under certain stress conditions and such that the resultant CDK muteins confer drought or salt stress tolerance to a plant, as the functional effect of amino acid substitution, including the substitution of non-phosphorylatable amino acids for phosphorylatable amino acids, will vary depending on the amino acid sequence of the protein, the position of the substituted amino acid in the sequence, and the amino acid substituted (See Krek W. et al. and Gould K.L. et al. set forth below). While the submitted reference of M.J. Betts and R.B. Russel (Exhibit B) teaches substitution preferences for tyrosine

and threonine, M.J. Betts and R.B. Russel (Exhibit B) do not describe the non-phosphorylatable amino acid residues that can be substituted for the phosphorylatable tyrosine or threonine residues that occupy the positions corresponding to residues 14 and 15 respectively in *Arabidopsis thaliana* CDKA;1.

Applicants also point in particular to Exhibit C, Hsieh J. et al. (Phosphorylation of the human vitamin D receptor by protein kinase C. Biochemical and functional evaluation of the serine 51 recognition site. J Biol Chem. 1993 Jul 15;268(20):15118-26), involving studies using the human vitamin D receptor (hVDR) which is selectively phosphorylated by protein kinase C-β (PKD-β). Applicants point out that previous studies by Hsieh J. et al. (1991) had shown that the serine 51 residue of human VDR (hVDR), which is conserved in all known VDRS, is selectively phosphorylated by protein kinase C-β (PKD-β) in vitro and in vivo. Applicants also point out that the authors found that alteration of serine 51 to a non-phosphorylatable (e.g. glycine, aspartic acid, or alanine) residue resulted in an approximately 60% reduction in basal hVDR phosphorylation in intact cells, and that mutation of serine 51 to threonine restored phosphorylation by PDK-B in vitro. Applicants further point out that Hsieh J. et al., in selecting Gly, Asp, or Ala to substitute for Ser, were following known principles for amino acid substitution as e.g., complied in Exhibit B. (reply page 10)

The Examiner maintains that a specific knowledge that the alteration of serine 51 to a non-phosphorylatable (e.g. glycine, aspartic acid, or alanine) residue in the hVD protein will result in an approximately 60% reduction in basal hVDR phosphorylation in intact cells, and that mutation of serine 51 to threonine in the hVD protein will restore phosphorylation by PDK-B in

vitro does not substitute for a description of the non-phosphorylatable amino acid residues that can be substituted for the phosphorylatable tyrosine or threonine residues that occupy the positions corresponding to residues 14 and 15 respectively in *Arabidopsis thaliana* CDKA;1 such that the resultant CDK muteins are not susceptible to inhibitory phosphorylation under certain stress conditions and such that the resultant CDK muteins confer drought or salt stress tolerance to a plant, as the functional effect of amino acid substitution, including the substitution of non-phosphorylatable amino acids for phosphorylatable amino acids, will vary depending on the amino acid sequence of the protein, the position of the substituted amino acid in the sequence, and the amino acid substituted (See Krek W. et al. and Gould K.L. et al. set forth below). While Hsieh J. et al. (Exhibit C) may have followed known principles for amino acid substitution, Hsieh J. et al. (Exhibit C) do not describe the non-phosphorylatable amino acid residues that can be substituted for the phosphorylatable tyrosine or threonine residues that occupy the positions corresponding to residues 14 and 15 respectively in *Arabidopsis thaliana* CDKA;1.

Applicants additionally point in particular to Exhibit D, McGraw T. et al. (Phorbol ester treatment increases the exocytic rate of the transferrin receptor recycling pathway independent of serine-24 phosphorylation. J Cell Biol. 1988 Apr;106(4):1061-6), who also performed experiments where the major protein kinase C phosphorylation site, Ser-24 on human transferring receptor (TR) was replaced with a non- phosphorylatable amino acid, Gly. Applicants point out that in this instance, the authors found that phosphorylation of Ser-24 is not

required for receptor functioning, and that McGraw et al. therefore, were also following known principles for amino acid substitution as e.g., complied in Exhibit B. (reply page 10)

The Examiner maintains that a specific knowledge that altering serine 24 to a non-phosphorylatable glycine residue in the human transferring receptor (TR) protein does not affect receptor functioning does not substitute for a description of the non-phosphorylatable amino acid residues that can be substituted for the phosphorylatable tyrosine or threonine residues that occupy the positions corresponding to residues 14 and 15 respectively in *Arabidopsis thaliana* CDKA;1 such that the resultant CDK muteins are not susceptible to inhibitory phosphorylation under certain stress conditions and such that the resultant CDK muteins confer drought or salt stress tolerance to a plant, as the functional effect of amino acid substitution, including the substitution of non-phosphorylatable amino acids for phosphorylatable amino acids, will vary depending on the amino acid sequence of the protein, the position of the substituted amino acid in the sequence, and the amino acid substituted (See Krek W. et al. and Gould K.L. et al. set forth below). While McGraw, T., et al. (Exhibit D) may have followed known principles for amino acid substitution, McGraw, T., et al. (Exhibit D) do not describe the non-phosphorylatable amino acid residues that can be substituted for the phosphorylatable tyrosine or threonine residues that occupy the positions corresponding to residues 14 and 15 respectively in *Arabidopsis thaliana* CDKA;1.

Applicants further point in particular to Exhibit E, Orr, J.W. and Newton, A.C. (Requirement for negative charge on "activation loop" of protein kinase C. J Biol Chem. 1994 Nov 4;269(44):27715-8). Applicants point out that in this study the authors produced mutants of

protein kinase C where Thr500 was mutated to either an acidic residue (Glu) or a neutral, non-phosphorylatable residue (Val). Applicants point out that substitution of Thr500 to Glu resulted in expression of a catalytically active protein kinase C in COS cells whereas mutation of Thr500 to a neutral, non-phosphorylatable residue (Val) resulted in expression of an inactive enzyme. (reply pages 10-11)

The Examiner maintains that a specific knowledge that substitution of Thr500 to Glu in protein kinase C produces a catalytically active protein kinase C whereas substitution of Thr500 to a neutral, non-phosphorylatable residue (Val) produces an inactive enzyme does not substitute for a description of the non-phosphorylatable amino acid residues that can be substituted for the phosphorylatable tyrosine or threonine residues that occupy the positions corresponding to residues 14 and 15 respectively in *Arabidopsis thaliana* CDKA;1 such that the resultant CDK muteins are not susceptible to inhibitory phosphorylation under certain stress conditions and such that the resultant CDK muteins confer drought or salt stress tolerance to a plant, as the functional effect of amino acid substitution, including the substitution of non-phosphorylatable amino acids for phosphorylatable amino acids, will vary depending on the amino acid sequence of the protein, the position of the substituted amino acid in the sequence, and the amino acid substituted (See Krek W. et al. and Gould K.L. et al. set forth below). While Orr J.W. and Newton, A.C. (Exhibit E) may have followed known principles for amino acid substitution, Orr J.W. and Newton, A.C. (Exhibit E) do not describe the non-phosphorylatable amino acid residues that can be substituted for the phosphorylatable tyrosine or threonine residues that occupy the positions corresponding to residues 14 and 15 respectively in *Arabidopsis thaliana* CDKA;1.

Applicants also point in particular to Exhibit F, Dong J. et al. (A phosphorylation site in the ftz homeodomain is required for activity. EMBO J. 1998 Apr 15;17(8):2308-18), who studied the *Drosophila* protein Fushi tarazu (Ftz). Applicants point out that during different developmental stages, the protein is heavily phosphorylated on different subsets of Ser and Thr residues, and that the authors demonstrated that mutagenesis of the Thr263 to a non-phosphorylatable residue Ala resulted in loss of ftz-dependent segments, whereas substitution of Thr263 with Asp, which is also non-phosphorylatable but which successfully mimics phosphorylated residues in a number of proteins, rescued the mutant phenotype. (reply pages 10-11)

The Examiner maintains that a specific knowledge that mutagenesis of the Thr263 to a non-phosphorylatable residue Ala resulted in loss of ftz-dependent segments, whereas substitution of Thr263 with Asp, which is also non-phosphorylatable but which successfully mimics phosphorylated residues in a number of proteins, rescued the mutant phenotype, does not substitute for a description of the non-phosphorylatable amino acid residues that can be substituted for the phosphorylatable tyrosine or threonine residues that occupy the positions corresponding to residues 14 and 15 respectively in *Arabidopsis thaliana* CDKA;1 such that the resultant CDK muteins are not susceptible to inhibitory phosphorylation under certain stress conditions and such that the resultant CDK muteins confer drought or salt stress tolerance to a plant, as the functional effect of amino acid substitution, including the substitution of non-phosphorylatable amino acids for phosphorylatable amino acids, will vary depending on the amino acid sequence of the protein, the position of the substituted amino acid in the sequence, and the amino acid substituted (See Krek W. et al. and Gould K.L. et al. set forth below). While

Dong J. et al. (Exhibit F) may have followed known principles for amino acid substitution, Dong J. et al. (Exhibit F) do not describe the non-phosphorylatable amino acid residues that can be substituted for the phosphorylatable tyrosine or threonine residues that occupy the positions corresponding to residues 14 and 15 respectively in *Arabidopsis thaliana* CDKA;1.

Applicants maintain that the studies provided herewith at Exhibits C-F demonstrate that as of the priority date of this application, April 21, 1998, skilled artisans were well aware of different non- phosphorylatable amino acids that could be substituted for tyrosine, threonine, or serine, and Applicants further submit that although the present application exemplifies the present invention with respect to having both the tyrosine at position 15 and the threonine at position 14 in CDKA;1 substituted with non-phosphorylatable amino acid residues, the present application's broader teaching for the use of a CDK comprising a non-phosphorylatable amino acid substituted for the relevant tyrosine has also been confirmed by the post-filing date literature. Applicants point in particular to Schuppler U. et al. (Effect of water stress on cell division and cell-division-cycle 2-like cell-cycle kinase activity in wheat leaves Plant Physiol. 1998 Jun;117(2):667-78), previously submitted as Exhibit C with Applicants' response filed December 2, 2003. Schuppler U. et al. repeatedly refer to the role of tyrosine phosphorylation in a plant CDK. Applicants also maintain that, as the remarks above and the Exhibits C-F show, the substitution of a non-phosphorylatable amino acid for a phosphorylatable amino acid at one position has been found to be sufficient in changing the activity of the relevant enzyme in many instances. (reply pages 11-12)

With respect to the post-filing date literature of Schuppler U. et al., the Examiner maintains that post-filing date literature cannot support the description of the claimed invention, as the invention must be described as of the filing date. With respect to Exhibits C-F showing that the substitution of a non-phosphorylatable amino acid for a phosphorylatable amino acid at one position has been found to be sufficient in changing the activity of the relevant enzyme in many instances, the Examiner maintains that a showing that the substitution of a non-phosphorylatable amino acid for a phosphorylatable amino acid at one position has been found to be sufficient in changing the activity of the relevant enzyme in many instances does not substitute for a description of the non-phosphorylatable amino acid residues that can be substituted for the phosphorylatable tyrosine or threonine residues that occupy the positions corresponding to residues 14 and 15 respectively in *Arabidopsis thaliana* CDKA;1 such that the resultant CDK muteins are not susceptible to inhibitory phosphorylation under certain stress conditions and such that the resultant CDK muteins confer drought or salt stress tolerance to a plant, as the functional effect of amino acid substitution, including the substitution of non-phosphorylatable amino acids for phosphorylatable amino acids, will vary depending on the amino acid sequence of the protein, the position of the substituted amino acid in the sequence, and the amino acid substituted (See Krek W. et al. and Gould K.L. et al. set forth below).

Applicants finally maintain that, with respect to the written description rejection, the Examiner has taken the position that the specification allegedly does not provide sufficient guidance with respect to which PSTAIRE comprising cyclin-dependent kinases other than CDKA;1 could, when appropriately mutated, be used to confer drought or salt stress tolerance to

a plant transformed therewith, and Applicants submit that this position is not based on fact. Applicants point in particular to the review article by Joubes J. et al. (CDK-related protein kinases in plants. Plant Mol Biol. 2000 Aug;43(5-6):607-20. Review), submitted as Exhibit D with Applicants' response filed December 2, 2003, which labels the plant gene family of CDKS having the PSTAIRE motif as the CDKA gene family, and which teaches that plant CDKA have a highly conserved amino acid sequence, with 89% similarity. Applicants also point out that Joubes J. et al. teach that the fifteen most conserved residues of eukaryotic serine-threonine and tyrosine protein kinases are conserved in plant CDKA, including the residues involved in the ATP-binding site and in regulatory phosphorylation, and that the residues involved in defining the consensus phosphorylation site of CDK, i.e., SPXK, where S is the phosphoacceptor, are also conserved in plant CDKA. Applicants additionally point out that most, if not all, of the genes encoding CDKS of the A type, set forth in Table 1 of Joubes J. et al. were available as of the priority date of the present application. (reply pages 12-13)

The Examiner maintains that the outstanding written description rejection was not predicated on the failure of the specification to provide sufficient guidance with respect to which PSTAIRE comprising cyclin-dependent kinases other than CDKA;1 could, when appropriately mutated, be used to confer drought or salt stress tolerance to a plant transformed therewith. The outstanding written description rejection was predicated on the failure of the specification to describe the genus of CDK muteins encoded by the nucleic acid molecules encompassed by the claims (pages 3-4 of the office action mailed February 24, 2004; pages 4-5 of the office action mailed June 3, 2003). The Examiner also maintains that Joubes J. et al. do not describe the CDK

muteins encoded by the nucleic acid molecules encompassed by the claims as Joubes J. et al. et al. describe only nonmutated CDKs.

Claims 1, 5-6, 10-11, 18-20, 22-26, 28-29 and 31 remain rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for obtaining plants tolerant to drought or salt stress conditions, said method comprising introducing into a plant cell, plant tissue or plant a nucleic acid sequence encoding an *Arabidopsis* CDC2a (CDKA;1) protein wherein the tyrosine at position 15 is substituted to phenylalanine and the threonine at position 14 is substituted to alanine, does not reasonably provide enablement for method comprising introducing into a plant cell, plant tissue or plant other nucleic acid sequences encoding other amino acid sequences, for the reasons of record set forth in the office action mailed February 24, 2004.

Applicant's arguments filed June 28, 2004 have been fully considered but they are not persuasive.

In response to the position of the Examiner, Applicants repeat, reassert and incorporate by reference the argumentation provided above as well as Exhibits A-F, reply page 13 which Applicants' maintain support their position that one skilled in the art having the present application as well as the literature extant as of the priority date of the application, would know which non-phosphorylatable amino acid residues to use in practicing the present invention. Applicants point in particular to page 5 of the office action mailed February 24, 2004 where the Examiner takes the position that the specification does not provide sufficient guidance with respect to how to use a PSTAIRE comprising cyclin-dependent kinase mutein having only the

tyrosine corresponding to position 15 in *A. thaliana* CDKA;I substituted with a non-phosphorylatable amino acid residue, and Applicants repeat and reassert the argumentation set forth above, where it was submitted that the application is replete with such teaching. Applicants also repeat and reassert that the law does not require a specific example of everything within the broad scope of the claims, and that, moreover, the law does not require any working examples. (reply pages 13-14)

The Examiner maintains that Exhibits A-F do not provide specific guidance with respect to which non-phosphorylatable amino acid residues may be substituted for the phosphorylatable tyrosine or threonine residues that occupy the positions corresponding to residues 14 and 15 respectively in *Arabidopsis thaliana* CDKA;1 such that the resultant CDK muteins are not susceptible to inhibitory phosphorylation under certain stress conditions and such that the resultant CDK muteins confer drought or salt stress tolerance to a plant. Such guidance is necessary because the functional effect of amino acid substitution, including the substitution of non-phosphorylatable amino acids for phosphorylatable amino acids, is unpredictable and will vary depending on the amino acid sequence of the protein, the position of the substituted amino acid in the sequence, and the amino acid substituted (See Krek W. et al. and Gould K.L. et al. set forth below).The Examiner also maintains that the specification only provides guidance for making and using sequences encoding the T14AY15F mutein of the *Arabidopsis* CDC2a (CDKA;1) protein.

The Examiner additionally acknowledges that the law does not require a specific example of everything within the broad scope of the claims, or working examples, but maintains that, in view of the broad scope of the claims which encompass the use of nucleic acids encoding any

CDK obtained from any source that comprises a PSTAIRE cyclin binding motif and that has any non-phosphorylatable amino acid residue substituted in a position that corresponds to the tyrosine located at position 15 in the amino acid sequence of *Arabidopsis thaliana* CDKA;1 or that further comprises any non-phosphorylatable amino acid residue substituted in a position that corresponds to the threonine located at position 14 in the amino acid sequence of *Arabidopsis thaliana* CDKA;1, and in view of the unpredictability in the art, guidance in excess of that disclosed would be required to practice the full scope of the claimed invention without undue experimentation.

In response to the Examiner's position that the specification does not provide sufficient guidance with respect to which PSTAIRE comprising cyclin-dependent kinases other than CDKA; 1 could, when appropriately mutated, be used to confer drought or salt stress tolerance to a plant transformed therewith, Applicants repeat, reassert, and incorporate by reference the argumentation set forth above and supported by Joubes J. et al. (CDK-related protein kinases in plants. Plant Mol Biol. 2000 Aug;43(5-6):607-20. Review), who teach

> "[t]he 31 plant CDKA have a highly conserved amino acid sequence, with 89% similarity (Figure 5). The fifteen most conserved residues of eukaryotic serine-threonine and tyrosine protein kinases are conserved in plant CDKA, including the residues involved in the ATP-binding site and in regulatory phosphorylation (Figure 5)."

Applicants maintain that most, if not all of the genes encoding CDKS of the A type, set forth in Table 1 of Joubes et al. (2000) were available as of the priority date of the present application.

(reply page 15)

The Examiner maintains that Exhibits A-F do not provide specific guidance with respect to which PSTAIRE comprising cyclin-dependent kinases other than CDKA;1 may be mutated such that the resultant CDK muteins are not susceptible to inhibitory phosphorylation under certain stress conditions and such that the resultant CDK muteins confer drought or salt stress tolerance to a plant.

The Examiner also maintains that Joubes J. et al. does not provide such guidance. While Joubes J. et al. teach the conservation of certain structural features among plant CDKAs, Joubes J. et al. do not teach that plant CDKAs are functionally interchangeable. Structurally homologous amino acid sequences are not always functionally interchangeable, and different PSTAIRE comprising CDKs are known to have different functional attributes. See, for example, Morgan D.O. (Cyclin-dependent kinases: engines, clocks, and microprocessors. Annu Rev Cell Dev Biol. 1997;13:261-91. Review), who teaches that the ability of CDK catalytic subunits to trigger cell cycle events is completely dependent on associated cyclin subunits, and that different PSTAIRE comprising CDKs are known to associate with different types of cyclins; e.g. CDC2 (CDK1) interacts with cyclin B during the M phase of mitosis, whereas CDK2 interacts with cyclin E during the G1/S phase of mitosis and cyclin A during the S phase and G2 of mitosis (page 262; page 264 Table 1). Morgan D.O. also teaches that cyclins are a remarkably diverse family of proteins wherein distant members of the family often seem barely related at the primary sequence level, that all CDKs do not bind all cyclins, and that there is considerable specificity in CDK-cyclin interactions (pages 267-268; page 273). Accordingly one cannot predict on the basis of structure alone which PSTAIRE comprising cyclin-dependent kinases other than CDKA;1

could, when appropriately mutated, be used to confer drought or salt stress tolerance to a plant transformed therewith.

In response to the Examiner's previous assertion that the effect of changing the amino acid composition of a PSTAIRE comprising cyclin-dependent kinase on its ability to confer drought or salt stress tolerance when expressed in a plant is unpredictable, and that absent such guidance, it would require undue experimentation for one skilled in the art to determine which PSTAIRE comprising cyclin-dependent kinases to modify and which non-phosphorylatable amino acid residues to use for their modification, in order to obtain nucleic acid molecules that would confer drought or salt stress tolerance to a plant transformed therewith, Applicants point out that it is settled law that it is not necessary that every last detail of an invention be described, by working examples or otherwise, and that the patent need not teach, and preferably omits, what is well known in the art. Applicants submit that, as exhaustively discussed above, one skilled in the art would know which PSTAIRE comprising cyclin-dependent kinase other than CDKA;1 could be used, and that based on the teachings of the prior art a skilled artisan would know which non-phosphorylatable amino acids would be suitable for substituting in a PSTAIRE comprising CDK. Applicants maintain that Exhibits C-F provide examples of prior art teachings where favored or neutral substitution preferences are taught, and that even if the final choice of what non-phosphorylatable amino acid to substitute for the tyrosine or threonine in a plant CDK in order to render that plant drought or salt stress tolerant requires some experimentation, such experimentation is not fatal under the provisions of 35 U.S.C. 112, first paragraph, as the foregoing remarks and the exhibits submitted herewith demonstrate that the determination of

which PSTAIRE comprising CDK to modify would not entail undue experimentation, and that the determination of which non-phosphorylatable amino acid residues to use for such modification in order to obtain nucleic acid molecules that would confer drought or salt stress tolerance would also not entail undue experimentation. (reply pages 15-16)

The Examiner acknowledges that it is not necessary that every last detail of an invention be described, by working examples or otherwise, but maintains that, in view of the broad scope of the claims which encompass the use of nucleic acids encoding any CDK obtained from any source that comprises a PSTAIRE cyclin binding motif and that has any non-phosphorylatable amino acid residue substituted in a position that corresponds to the tyrosine located at position 15 in the amino acid sequence of *Arabidopsis thaliana* CDKA;1 or that further comprises any non-phosphorylatable amino acid residue substituted in a position that corresponds to the threonine located at position 14 in the amino acid sequence of *Arabidopsis thaliana* CDKA;1, and in view of the unpredictability in the art, guidance in excess of that disclosed would be required to practice the full scope of the claimed invention without undue experimentation. The Examiner also acknowledges that the patent need not teach, and preferably omits, what is well known in the art, but maintains that it is not well known in the art which PSTAIRE comprising cyclin-dependent kinases other than CDKA;1 may be mutated such that the resultant CDK muteins are not susceptible to inhibitory phosphorylation under certain stress conditions and such that the resultant CDK muteins confer drought or salt stress tolerance to a plant, or which non-phosphorylatable amino acid residues may be substituted for the phosphorylatable tyrosine or threonine residues that occupy the positions corresponding to residues 14 and 15 respectively in *Arabidopsis thaliana* CDKA;1 such that the resultant CDK muteins are not susceptible to

inhibitory phosphorylation under certain stress conditions and such that the resultant CDK muteins confer drought or salt stress tolerance to a plant.

The Examiner maintains that, as set forth above, one skilled in the art would not know which PSTAIRE comprising cyclin-dependent kinase other than CDKA;1 could be used, as one cannot predict on the basis of structure alone which PSTAIRE comprising cyclin-dependent kinases other than CDKA;1 could, when appropriately mutated, be used to confer drought or salt stress tolerance to a plant transformed therewith, as structurally homologous amino acid sequences are not always functionally interchangeable, and different PSTAIRE comprising CDKs are known to have different functional attributes.

The Examiner also maintains that a skilled artisan would not know which non-phosphorylatable amino acids would be suitable for substituting in a PSTAIRE comprising CDK such that the resultant CDK muteins are not susceptible to inhibitory phosphorylation under certain stress conditions and such that the resultant CDK muteins confer drought or salt stress tolerance to a plant, as one cannot predict on the basis of a general knowledge of which types of substitutions are more favorable than others for the phosphorylatable tyrosine or threonine which specific non-phosphorylatable amino acid residues may be substituted for the phosphorylatable tyrosine or threonine residues that occupy the positions corresponding to residues 14 and 15 respectively in *Arabidopsis thaliana* CDKA;1 such that the resultant CDK muteins are not susceptible to inhibitory phosphorylation under certain stress conditions and such that the resultant CDK muteins confer drought or salt stress tolerance to a plant, as the functional effect of amino acid substitution, including the substitution of non-phosphorylatable amino acids for phosphorylatable amino acids, is unpredictable and will vary depending on the amino acid

sequence of the protein, the position of the substituted amino acid in the sequence, and the amino acid substituted.

See, for example, Krek W. et al. (Mutations of p34cdc2 phosphorylation sites induce premature mitotic events in HeLa cells: evidence for a double block to p34cdc2 kinase activation in vertebrates. EMBO J. 1991 Nov;10(11):3331-41), who evaluated the effect of substituting Thr14 and/or Tyr15 in the PSTAIRE comprising CDK $p34^{cdc2}$ with the nonphosphorylatable amino acids alanine and phenylalanine. Krek W. et al. observed significant differences in the effect of expressing different CDK $p34^{cdc2}$ muteins on Histone H1 kinase activity and cell cycle progression in HeLa cells. Histone H1 kinase activity associated with wild-type CDK $p34^{cdc2}$ and the T14A mutein was very low at all times after transfection, whereas Histone H1 kinase activity associated with the T14AY15F mutein rapidly increased with time after transfection, and Histone H1 kinase activity associated with the Y15F mutein increased with time after transfection but followed a time course different from that of the T14AY15F mutein (pages 3333-3334 and Figure 5). The morphology of cells transfected with wild-type CDK $p34^{cdc2}$ and the T14A mutein displayed a normal interphase phenotype, whereas expression of the T14AY15F mutein induced premature entry into mitosis in ~35% of transfected cells as early as 8 hours post-transfection with the proportion of mitotic cells reaching almost 80% by 16 hours, and expression of the Y15F mutein induced premature entry into mitosis in <5% of transfected cells at 8 hours post-transfection with the proportion of mitotic cells reaching only 25% by 16 hours (pages 3334-3335 and Figures 6-9).

See also, for example, Gould K.L. et al. (Characterization of novel mutations at the *Schizosaccharomyces pombe* cdc2 regulatory phosphorylation site, tyrosine 15. Mol Biol Cell.

1996 Oct;7(10):1573-86), who evaluated the effect of substituting Tyr15 in the PSTAIRE comprising CDK cdc2p from *S. pombe* with the phosphorylatable amino acids serine and threonine and the nonphosphorylatable amino acids phenylalanine and glutamic acid. Gould K.L. et al. teach that while the Y15E cdc2p mutein was nonfunctional as expected, the Y15E cdc2p mutein failed to mimic constitutive phosphorylation at position 15 as had been previously exemplified for the PSTAIRE comprising CDK CDC2 from humans (page 1574; page 1584). Gould K.L. et al. also teach that while the Y15T and Y15S cdc2p muteins could not be phosphorylated at position 15, the Y15T and Y15S cdc2p muteins were unlike the Y15F cdc2P mutein (which is also not phosphorylated at position 15), as the Y15T and Y15S cdc2p muteins behave as dominant-negative mutations, whereas the Y15F cdc2P mutein behaves as a gain-of-function mutation (page 1574). Gould K.L. et al. additionally teach that unlike several previously described dominant-negative mutants of cdc2p, the Y15E, Y15T and Y15S cdc2p muteins retained protein kinase activity in vitro, and were capable of initiating some, but not all, events of mitosis (page 1574). Gould K.L. et al. further teach that overexpression of the Y15E, Y15T and Y15S cdc2p muteins confers different phenotypes on cells, and that their data coupled with previous results indicate that quite distinct phenotypes can be obtained by altering Y15 to different amino acid residues, which serves as another reminder that caution should be exercised when interpreting experimental results based on the behavior of site-directed mutants (page 1584).

In the instant case the specification does not provide sufficient guidance with respect to which PSTAIRE comprising cyclin-dependent kinase other than CDKA;1 could be used, or with respect to which specific non-phosphorylatable amino acid residues may be substituted for the

phosphorylatable tyrosine or threonine residues that occupy the positions corresponding to residues 14 and 15 respectively in *Arabidopsis thaliana* CDKA;1, such that the resultant CDK muteins are not susceptible to inhibitory phosphorylation under certain stress conditions and such that the resultant CDK muteins confer drought or salt stress tolerance to a plant. Absent such guidance one skilled in the art would have to make a variety of different mutein coding sequences by substituting different types of non-phosphorylatable amino acid residues at positions corresponding to residues 14 and 15 respectively in *Arabidopsis thaliana* CDKA;1 in different types of PSTAIRE comprising CDKs and test each mutein coding sequence for its ability to confer drought or salt stress tolerance to a plant in order to discriminate between operative and inoperative embodiments encompassed by the claims. Such a trial and error approach to practicing the claimed invention would constitute undue experimentation.

Claim Rejections - 35 USC § 102

Claims 25-26, 28-29 and 31 remain rejected under 35 U.S.C. 102(b) as being anticipated by Hemerly A. et al. (Dominant negative mutants of the Cdc2 kinase uncouple cell division from iterative plant development. EMBO J. 1995 Aug 15;14(16):3925-36, Applicant's IDS), for the reasons of record set forth in the office action mailed February 24, 2004, and the reasons set forth below.

Applicant's arguments filed June 28, 2004 have been fully considered but they are not persuasive.

Applicant argues that the amendment of the claims to delete reference to a chimeric promoter should overcome the rejection (reply page 17).

The amendment of the claims to delete reference to a chimeric promoter does not overcome the rejection as the CaMV 35S promoter used by Hemerly et al. is abiotic stress inducible in that it is known to function under conditions of abiotic stress, and is tissue-specific in that it exhibits higher levels of activity in some tissues as compared to other tissues.

Remarks

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Cynthia Collins whose telephone number is (571) 272-0794. The examiner can normally be reached on Monday-Friday 8:45 AM -5:15 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Amy Nelson can be reached on (571) 272-0804. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

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Cynthia Collins
Examiner
Art Unit 1638

CC

Cynthia Collins 1/27/05